Award Number: W81XWH-10-1-0736

TITLE: Objective Methods to Test Visual Dysfunction in the Presence of Cognitive Impairment

PRINCIPAL INVESTIGATOR: Randy Kardon M.D. Ph.D.

CONTRACTING ORGANIZATION: University of Iowa, Iowa City IA 52242

REPORT DATE: October 2012

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
1 October 2012	Annual	September 15 2011-September 14 2012

4. TITLE AND SUBTITLE
Objective Methods to Test Visual Dysfunction in the Presence of Cognitive of Cognitive Impairment

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0736

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Randy Kardon, M.D., Ph.D., Pieter Poolman, Ph.D.

E-Mail: randy-kardon@uiowa.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Iowa, The
105 Jessup Hall
Iowa City, IA 52242-1316

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Purpose: to develop and validate objective tests to diagnose vision deficits in patients with cognitive impairment and ensure effective monitoring of treatment.
Scope: objective methods to monitor vision include 1) the pupil light reflex, 2) light evoked potentials from the brain and from the eye and 3) purposeful eye movements to track moving targets that are resolved.
Major Findings (year two): 1) a prototype, dry electrode system was delivered in Year 2 and was evaluated with specified requirements met, 2) a Smart Eye head and ocular tracking system was further tested and optimized in conjunction with a high contrast, high luminance 55" monitor for presenting visual stimuli for eye movement, pupil responses and cortical visual evoked potentials (VEPs), 3) a software architecture (matrix approach) for regional visual field stimulus presentation, data synchronization, and analysis from visual cortical responses recorded from scalp electrodes was developed and completed.
Significance: objective tests of vision based on eye tracking of visual targets, pupil responses, and cortical visual evoked potentials will greatly improve eye care by providing faster, lower cost testing that can be performed in remote settings and will provide a new tool for assessing innovative treatments being developed to save or restore vision.

15. SUBJECT TERMS
Traumatic brain injury, cognitive dysfunction, pupil light reflex, eye movements, evoked potentials, visual function

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	25	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

	Page
Introduction……..…..	**4**
Body…….	**5**
Key Research Accomplishments……..	**24**
Reportable Outcomes……	**24**
Conclusion……	**24**
References……	**25**
Appendices……	**25**

INTRODUCTION: Our project's research goal is to provide an objective and military relevant means for diagnosing and localizing the site of visual dysfunction in cognitively impaired patients. The successful attainment of this goal hinges on the development of a suite of objective tests designed to free the TBI patients from the cognitive demands placed on them during standard visual testing. As a necessary step for testing of cognitively impaired patients with suspected visual dysfunction, we will first optimize three objective tests of visual function: a) pupil contractions to light stimuli, b) evoked potentials elicited from the visual cortex in response to visual stimuli in the central and peripheral visual field locations, and c) eye position correlated with moving visual targets varying in spatial properties as a means of verifying that the patient was able to perceive the targets. Next, we will validate these objective tests against gold standard behavioral tests of visual field sensitivity in cognitively intact participants who are capable of performing these tests accurately. For the validation phase, participants will be selected who have either normal visual function or who have known dysfunction at different sites along their visual pathway. Using this strategy, normal eyes and eyes with well-defined damage to the retina, optic nerve, visual radiations or visual cortex will be used to study the sensitivity and specificity of the different modalities of objective testing being evaluated in this proposal. Once validated in these participants, these objective tests can then be rapidly implemented for use in cognitively impaired patients, specifically those who have suffered traumatic brain injury.

BODY - RESEARCH ACCOMPLISHMENTS ASSOCIATED WITH APPROVED STATEMENT OF WORK FOR YEAR 2:

Task 1. Implementation of novel product-ready hardware solutions that allow objective testing of the visual system (months 1-12):

1a. Hand-held portable pupillometer (Neuroptics, Inc.) (months 12-24).

The hand-held portable pupillometer (Neuroptics) which was able to deliver white light stimuli and record pupil movements in response to light stimuli for diagnosing retinal and optic nerve disorders has now been replaced by a small desktop unit that is binocular (delivers stimuli to each eye and collects pupil responses from both eyes simultaneously). This will allow afferent visual abnormalities to be differentiated from efferent disorders of the output pupil pathway. The new unit (Neuroptics Inc, Irvine, CA) also detaches for use at bedside exam. This unit also delivers chromatic light stimuli (blue, red, green or white) so that rod, cone and intrinsic melanopsin retinal ganglion cell activation can be derived for differentiating visual loss from photoreceptor disease from that of optic nerve/anterior visual pathway diseases. We are presently redesigning testing protocols to take advantage of this incorporated feature and to reduce testing time to a minimum (one minute):

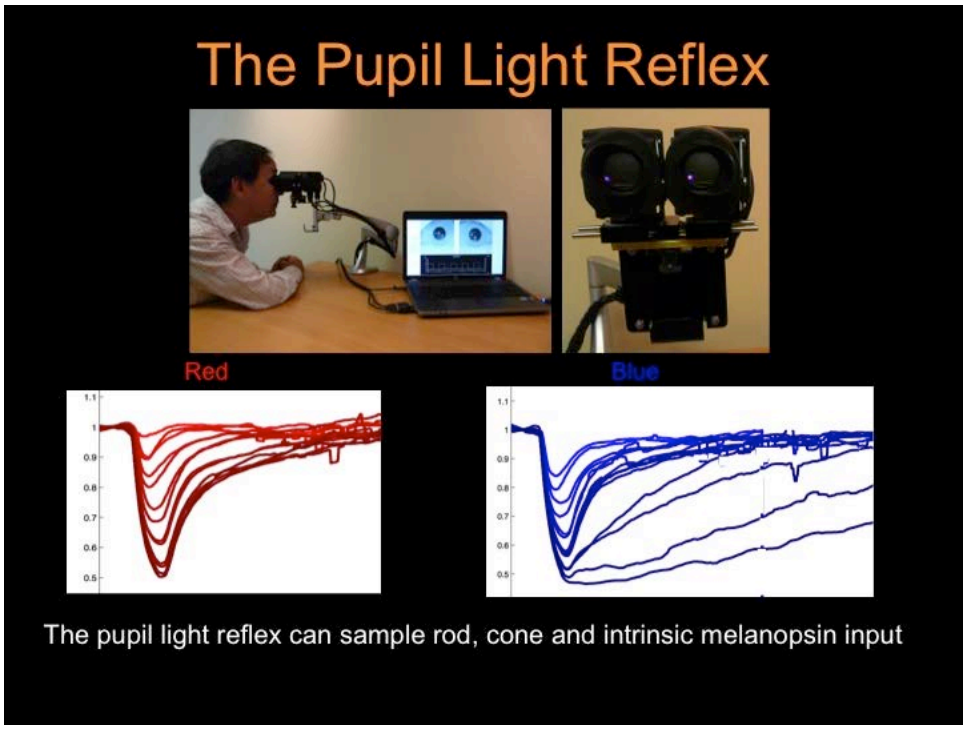


Figure 1. Recent work with binocular chromatic (red and blue light stimuli) showing rod, cone and melanopsin mediated pupil responses. Top is a newly developed desktop unit that can record both pupils and stimulate either the right eye, left eye or both eyes with red, blue, green or white light. At bottom

are a series of pupil light reflex waveforms with increasing intensity of red light for cone responses (red tracings) and blue light responses (blue tracings) for rod mediated responses at low intensity and sustained pupil contractions from melanopsin mediated responses to blue light at the hightest intensities.

In addition, in response to our suggestions, Neuroptics is currently developing a lightweight wearable portable pupillometer that can deliver red, blue or white light stimuli to either eye and can also record from both pupils at the same time. This unit is fully portable, battery powered and self contained and could be used in a variety of environments. We have been helping the company with the design of the prototype which is anticipated to be delivered for our use in Year 3:

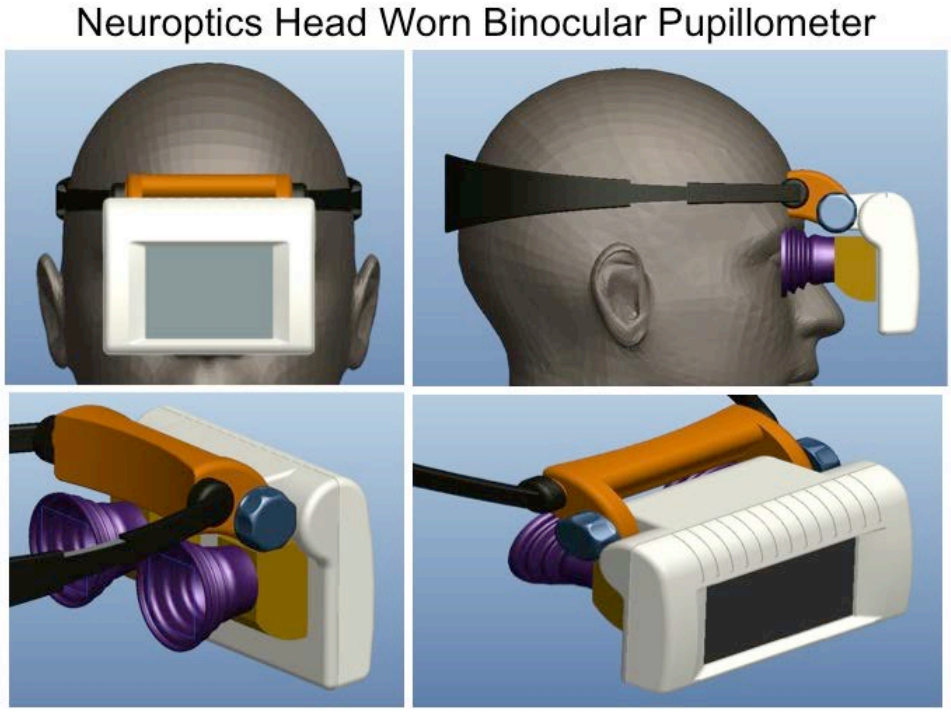


Figure 2. Prototype design of fully portable, battery powered binocular pupillometer that can deliver chromatic stimuli to one or both eyes and record pupil responses from both eyes. This prototype, based on hardware and software that we are enabling in the desktop unit shown in Figure 1, is being manufactured by Neuroptics Inc (Irvine, CA) and is expected to be available for testing in year 3.

1b. TrueField Analyzer visual field testing device (Seeing Machines Limited)

The TrueField Analyzer that has been developed by Dr. Ted Maddess at Canberra University in Australia for Seeing Machines Limited has still not been commercially released for patient testing at this time. I visited their laboratory in September 2011 in Australia and they are still unable to provide us with a date when the instrument

will be available for use and purchase. Because of the uncertainty surrounding the deliverability of the TrueField Pupil Visual Field Analyzer, we have now developed a flexible visual stimulation software platform that allows us to measure pupil responses to focal stimuli in different locations of the visual field, so that we can still proceed with collecting pupil responses to diffuse and focal stimuli in normal subjects and patients with our own instrumentation. Developing our own regional visual field pupil perimetry testing will enable us to still pursue this type of testing.

1c. "Dry electrode" wireless EEG system (Sigmed, Inc.) (months 7-12) –acquired in year 2 and being integrated into our testing device in year 3:

We received our dry-electrode wireless system during the last half of year 2.
At our request, Sigmed redesigned their current 16-channel EEG system to accommodate our requirements to measure from 8 channels placed around the eyes to measure EOG, orbicularis-corrugator EMG, ERG, and another 8 channels placed over occipital-parietal-temporal scalp locations to measure evoked potentials from visual cortex.

Figure 3: **New wireless "dry" electrodes for facial/brow/lower eyelid muscle EMG and ERG recording which are squares and are sponge-like (left). Rounded, spring-loaded dull prong electrodes for the scalp are shown to the upper right, that can penetrate around hair follicles for recording EEG/visual evoked potentials.**

The requirements that are being met to make the system work with our existing equipment and planned testing are:

1) The dry electrode wireless system replaces the wired Biopac modules currently used to collect the same electrophysiological measures. The new system has the advantage of being wireless, no skin preparation or gel is needed at the point of contact with skin, there is a large dynamic range of potential that can be recorded (24 bits, +/- 2.5 volts), and it will allow a much faster set-up time for the proposed experiments. The new type of dry electrode will be more comfortable for the patient and easy to apply. We are currently designing a flexible scalp band and face band to hold the electrodes in place for both visual evoked potentials recorded from the occipital scalp area over visual cortex and for recording the electroretinogram (ERG), electro-oculogram (EOG) and electromyogram (EMG) from orbicularis and brow muscles in response to visual stimuli. Mark Ginsberg, one of our local jewelry story owners has acquired 3D extruding printers for medical instrumentation applications and will be contracted to refine the design of the electrode holder and will be able to extrude different prototypes to allow us to design and implement a comfortable and effective face/eye mask (similar to the outer rim of swimming goggles) that will hold the electrodes which are mounted on sponge-like material against the skin.
2) Method to synchronize the onboard system clock with an external time server via wireless link (e.g., basic NTP client functionality).
3) Time-stamping of each recorded EEG/ EMG time-slice.
4) Specification of software interface:
    (a) API to send commands/receive responses from system,
    (b) Streaming data API,
    (c) Data packet layout.
5) Two different types of dry electrodes (not requiring skin preparation or electrode gel), configured to be clipped on or off the electrode wiring ends:
    (a) 8 electrodes -soft fabric-over-sponge (for facial locations),
    (b) 8 electrodes -hair penetrating (scalp locations).

6) Low impedance (5-10 kilo-ohms)

The new low impedance electrodes allow us to take advantage of the low noise for a very high signal to noise ratio.

1d. Multi-camera eye movement monitor (Smart Eye AB) and visual stimulus software platform (months 1-24)

Visual stimulus presentation system and software platform

In year 2, we received the super bright large-screen display system (based on a 55" 1920 x 1080 LED TV platform) from DynaScan Technology, Inc. in Irvine, CA. This monitor is unique to other visual displays because it can deliver a maximum white level brightness of 5,000 cd/m^2, compared to 300-700 cd/m^2 for standard TVs and monitors. We calibrated this monitor and successfully tested out our software that was written by Dr. Poolman to control the brightness, duration, spatial features, location, and color for each visual stimulus that will be presented during testing for

eliciting pupil responses (in addition to the desktop and portable units shown in Figures 1 and 2), eye movements and evoked potentials.

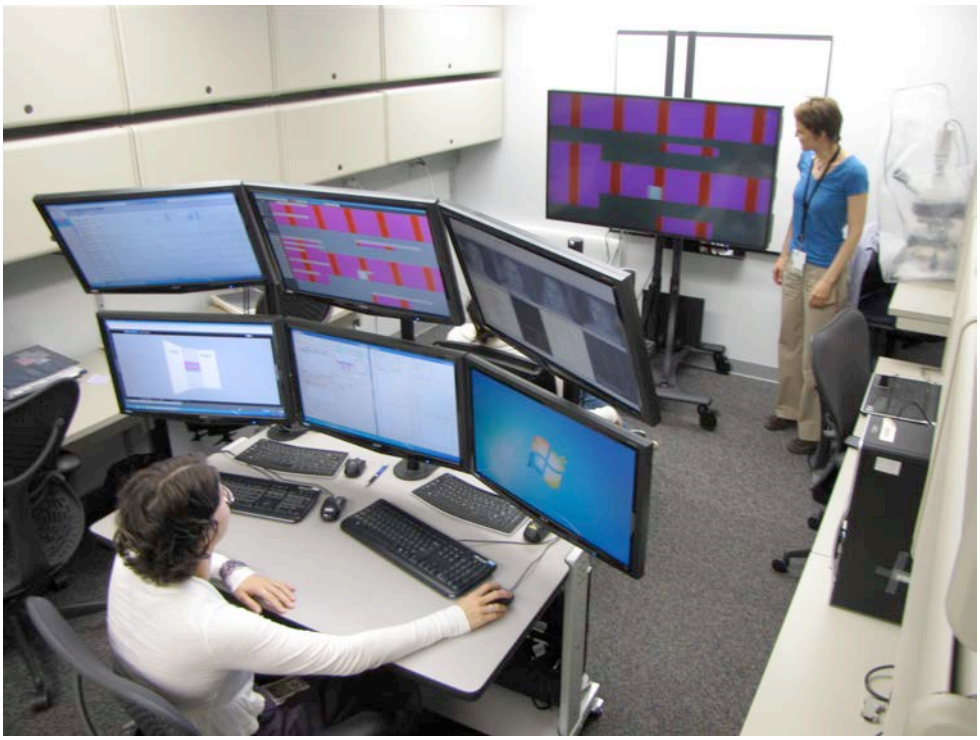


Figure 4: **Integrated visual stimulus and analysis platform for recording eye movements, pupil movements and evoked potentials**

This monitor and software enables us to use the same display unit to present both bright chromatic stimuli for pupil light reflex measurements, as well as present moving targets for eye movement and pattern stimuli for evoked response (VEP) tests. A combined stimulus presentation system allows for a reduction in testing times through leveraging the same infrastructure for all three testing paradigms (pupil, eye movements and electrical responses to visual stimuli), and reduce the footprint of the test equipment.

We have spent a significant effort to consolidate the processes of running an experiment, data recording, and data analysis into a single workflow of operational steps for the pupil light reflex test. The workflow architecture allows us to launch, pause, and monitor the stimulus presentation and data collection processes, as well as data analysis – both real time (on-the-fly), and in post-processing (after-action review) mode – from a set of interacting Matlab graphical user interfaces (GUIs). The real-time (on-the-fly) analysis provides us with the ability to decide whether to delay or repeat a stimulus based on the subject's responses. The workflow architecture is specifically designed to be easily extendible to the other modalities of tests, physiological responses, and analysis requirements and we plan to continue with this development effort in the next quarter. Screenshots of the Experiment Manager and Pupil Analysis GUIs are shown below. Apart from selecting, launching,

and controlling experiments, the user can also set parameters and select rules to govern when the next stimulus is to be presented to the subject.

For example, in the case of pupil light reflex recordings, the Experiment Manager can be instructed to use time duration after a stimulus and/or recent pupil size to automatically advance to the next stimulus. The user is also allowed to interrupt (pause) this automatic process, or to force the presentation of any stimulus if needed. In the Pupil Analysis GUI, the user can select and set numerous parameters to control the analysis and visualization of stimulus-response metrics. The analysis is agnostic as to whether data are streaming to the GUI (real-time mode) or are loaded from a static data source of previously recorded data (post-processing mode). Both GUIs are also agnostic as to the origin of the pupil and eye tracking data, and can deal with data from both our Arrington and Smart Eye eye movement/pupil movement systems. The same will be true for EEG and EMG data, which will be allowed to originate from either the Biopac or the new dry electrode system.

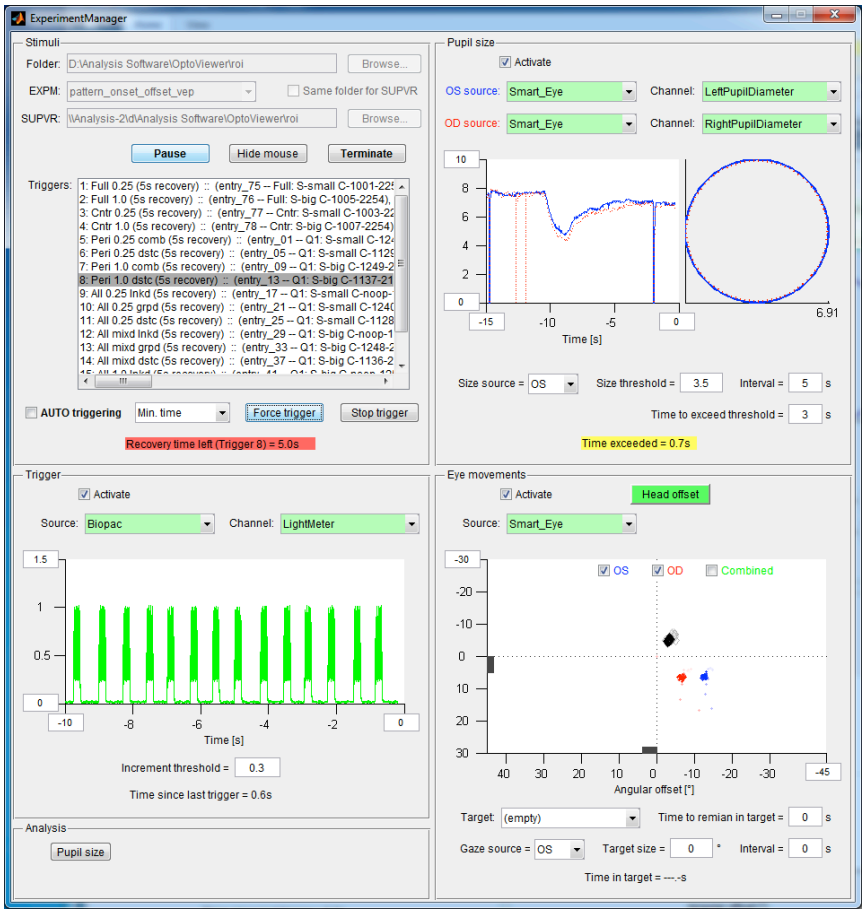


Figure 5. Updated layout of the Experiment Manager GUI. In the upper right portion of the window is the real-time pupil data display from the right and left eye recording in relation to a light stimulus. The red and blue circles are a graphical display of the instantaneous right and left pupil size, superimposed, which change in real time as the data is streaming onto the display. The Pupil Analysis GUI can be launched at any time with the "Pupil size" button in the "Analysis" panel (lower left portion of window). The lower right portion of window is used to display real-time head and eye tracking measurements, as well as a user-specified fixation target. The most recent few seconds of the orientation of the left, right, and/or combined gaze vectors, as well as the orientation of the current stimulus (black diamond) are depicted in the graph to assist the experimenter in visualizing the subject's viewing behavior with respect to the stimulus. Furthermore, based on whether the subject is fixating a pre-specified target, the experimenter can control the onset of stimuli, either manually, or in an automated way based on a set of rules. Please see the text for additional details.

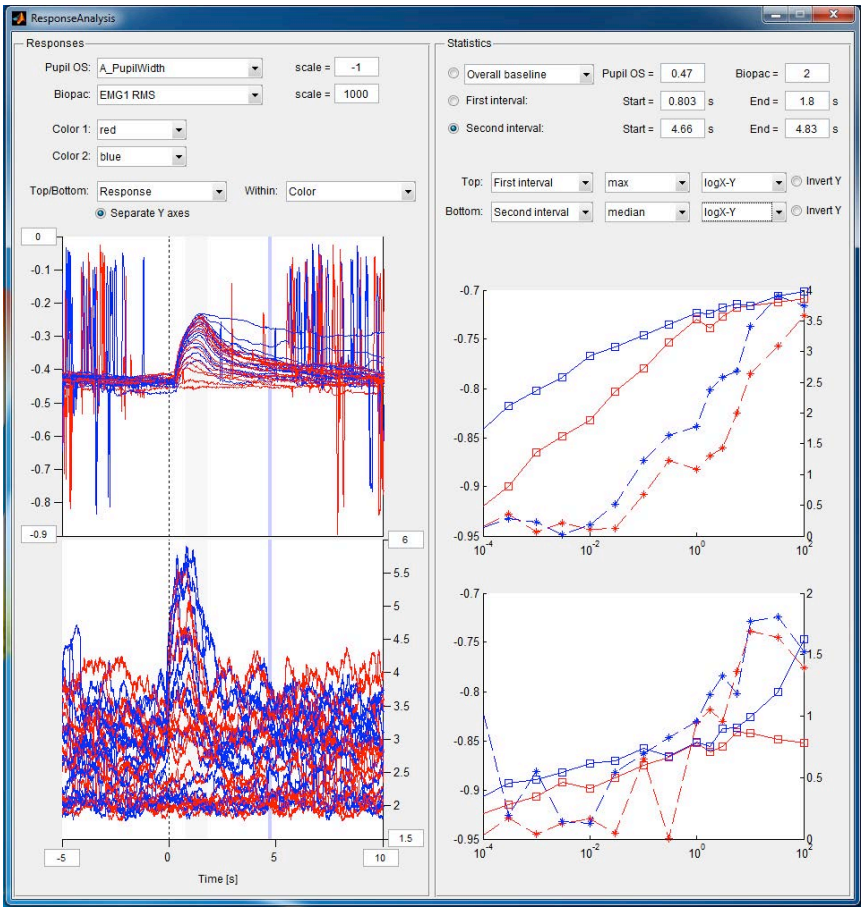


Figure 6. Updated layout of the Response Analysis GUI. The GUI can now be used to analyze responses from either a single data modality or from two different data modalities. For the example shown in the figure, the GUI is used for analyzing pupil light reflex and procerus/corrugator EMG data. This interface allows the user to define how the raw signal (in this case left pupil size time series as a function of light intensity, shown in upper left panel, and the EMG time series, shown in the lower left panel) should be analyzed and displayed in real time or after the experiment is over, playing back the data stream. The pupil movements and EMG responses are respectively superimposed for red and blue light stimuli of increasing intensity. For example, shown in the upper right panel is the maximum change in pupil size (solid lines) and EMG responses (dashed lines) recorded as a function of log light intensity of light stimuli. As the light intensity increases, so does the amplitude of the pupil movement and EMG response. In real time, points would appear on the graph as the data is collected to allow the user to evaluate the results in real time and repeat any portion of the experiment while the subject is still present. The lower right panel shows the sustained pupil contraction and EMG responses present at about 5 seconds after the one second stimulus onset. This shows that for the blue light stimuli at brighter intensities, the pupil response is more sustained (blue squares and solid line) compared to the responses to red light stimuli (red squares and solid line). Please see the text for additional details.

We have also developed a software tool to quickly create vanishing optotypes from various pre-existing images of an object of interest. The process starts with turning the image of the object into a line drawing. The user then sets the line widths and contrast levels to define the appearance of the vanishing optotype. An example of a vanishing optotype from our collection is shown below which was made from a picture of an armed enemy soldier.

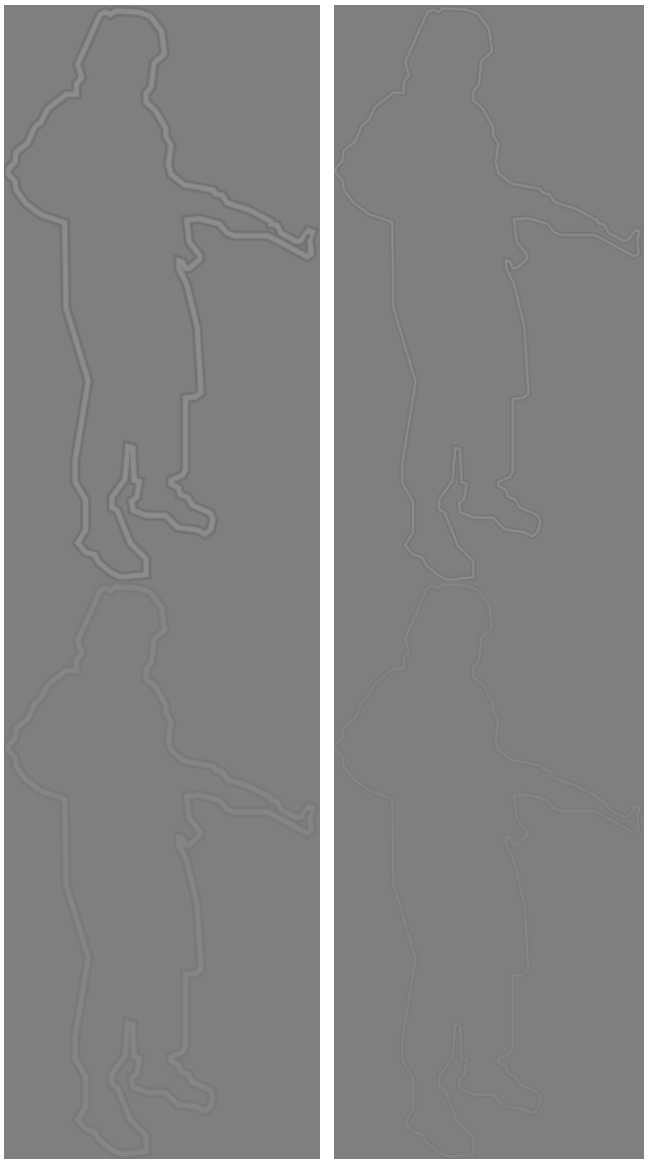


Figure 7. Vanishing optotypes of an armed person based on different line widths (left vs. right), and contrast levels (top vs. bottom). In the top section the original image is rendered into a thick-lined optotype (left) and a thin-lined optotype (right). In the bottom panel each of the images are rendered as a lower contrast line drawing with the features of the vanishing optotype. At this lower contrast the thinner lined drawing starts to disappear in the lower right panel.

As reported in an earlier Quarterly Report during year 2, we have implemented a temporally modulated stimulus for the visually-evoked potential (VEP) portion of this project, with the objective to measure regional visual field responses from evoked responses elicited from the eye and brain. The advantage of using such a stimulus is that it will allow us to interrogate the visual system's ability to conduct impulses in the central visual field, but also simultaneously in other locations in the peripheral vision. This is accomplished by using a matrix stimulus paradigm that correlates responses with specific temporal frequencies of visual stimuli occurring independently in each region of the visual field being tested. The test can be potentially performed on multiple platforms, such as tablets and smartphones, which could be used to evaluate traumatic brain injury patients in the field.

To complement the existing frequency-modulated checkerboard stimuli, we have now also added a set of flash and pattern onset/offset stimuli based on the International Society for Clinical Electrophysiology of Vision (ISCEV) 2009 standard. For pattern onset/offset, the checkerboard pattern is abruptly exchanged with a diffuse gray background. Pattern onset duration is set at 200ms, as specified by the ISCEV standard. Onsets are separated by at least 400ms of diffuse background. This paradigm differs from our earlier VEP stimulus paradigm in an important way: for the frequency-modulated stimuli, each stimulus location is assigned a different distinct temporal frequency to facilitate differentiation of the responses amongst the central and peripheral visual areas, while we rely on the exact stimulus onset times in case of the ISCEV-type stimuli to separate out the responses from the different visual areas, as explained later on. Two pattern element sizes -- checks of 0.25° or 1° per side -- can be used in a mix-and match approach to populate the different stimulus locations based on the subject's acuity level.

Ideally, the mean luminance of the diffuse background and the checkerboard is set to be identical with no change of luminance during the transition from pattern to diffuse blank screen. This is difficult to achieve on a LCD type monitor as the gray-to-white time interval is inherently different from the gray-to-black time interval (similarly, white-to-gray and black-to-gray time intervals) giving rise to faint millisecond-long flashes every time the stimulus changes from a diffuse background to a checkerboard pattern and vice versa. Nonetheless, through the use of a diffuser, care is taken to ensure that the steady-state mean luminance of the diffuse background matches the steady-state mean luminance of the checkerboard pattern. It is important to note that the ISCEV standard is solely geared towards a single full-field stimulus, while it is our stated goal to develop and test a VEP paradigm which will enable us to interrogate multiple broad locations of a subject's field of view within a short time period, which will be especially useful when testing cognitively-impaired patients in future studies. Although multi-focal techniques exist, they are too fine-grained for our purposes, and take an enormous amount of time to allow for the presentation of enough stimulus repetitions for data analytic purposes.

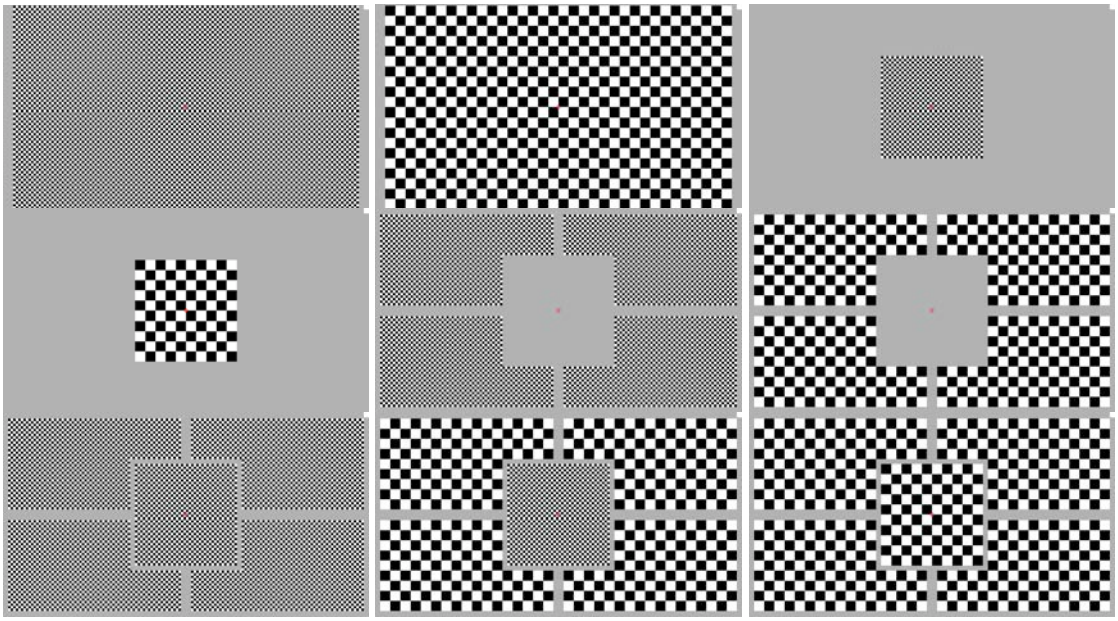


Figure 8. Examples of nine (9) different checkerboard layouts using 0.25° and 1° check sizes to create full-field, center-only, peripheral-only, and combined center-peripheral stimuli. A red circle is provided in the center of the screen to serve as a fixation target for the subject during the stimulation sequence.

In order to design the temporal characteristics of the VEP stimulus sequence to ensure that we can successfully extract the responses from simultaneous multi-focal and overlapping stimuli, we have considered the assumptions and implications of numerous methodologies referenced in literature. One of the most well-known methods for functional testing of sensory and other neural pathways is the evoked response potential (ERP) or transient response (TR) methodology. ERPs (or TRs) require the use of time-domain conventional averaging to improve poor signal-to-noise ratio, commonly due to artifact contamination, which results in longer acquisition periods to record additional responses. In spite of its advantages, conventional averaging has a severe limitation: If the response to each stimulus is not complete prior to the presentation of the next stimulus, it results in overlapping responses and the difficulty to separate responses into their corresponding components. As a consequence of this limitation, the stimulation rate for EP (or TR) paradigms is limited by the duration of the recorded physiological response.
In an effort to circumvent this time duration limitation, faster stimulation rates can be achieved through the use of steady-state responses (SSRs). SSR acquisition uses the same averaging techniques with a constant stimulus rate and no jitter. Under these conditions the responses overlap each other, resulting in a complex waveform that is instead analyzed in the frequency domain by measuring spectral peaks. In a steady-state condition, the characteristics of the overlapping responses depend on the sensitivity of the responses at the stimulation rate. Also, critical information provided by the waveform morphology and components are lost due to the overlapping responses and the periodic nature of the stimulus sequence. Note that

our frequency-modulated checkerboard stimulus paradigm is an example of the SSR technique.

A second technique to circumvent the limitations imposed by conventional averaging is the use of specially designed stimulus sequences called maximum length sequences (MLS), which allows one to separate an individual response from overlapping responses. Other researchers have proofed the validity and reliability of the MLS method and the existence of other similar sequences such as the Legendre sequences. These studies also showed that the response generation was likely to be the same as in conventional averaging. However, a major limitation of the MLS method is rooted in its limited choice of sequences. These sequences cover a wide range of rates with a high degree of jitter. Since ERP or TR adaptation effects differ widely in different neurosensory systems, the interpretation of MLS-generated responses could be difficult.

To summarize the findings from literature, the ERP (or TR) method cannot be used for fast stimulus rates due to overlap of responses, and the SSR method cannot be used for analyzing the characteristics of the individual responses due to overlap. The MLS and other similar methods solve the problem of component decomposition only for a few special stimulus sequences. These special sequences have a wide range of jitter, which limits the usefulness of the method in different applications. The temporal design of our latest VEP stimulus sequence, as well as the analysis method needed to extract the responses from simultaneous multi-focal and overlapping stimuli, draw heavily on principles used in the field of functional magnetic resonance imaging (fMRI). Given the long duration of the hemodynamic response function (HRF) -- blood oxygenation changes occur up to 15s following a stimulus -- and significant costs associated with operating MR equipment, fMRI researchers have adapted the generalized least squares (GLS) method to deconvolve overlapping stimulus responses, which allows them to design shortened stimulus sequences which are not boring, while minimizing anticipation and habituation. The latter benefit is also a result of the need to use a wideband, noise-like stimulus onset sequence for estimation of the HRF wave shape. The main assumption of the GLS model implies that the individual response to each stimulus is independent of other stimuli and responses, and that the measured overall response is a superposition or arithmetic sum of the individual overlapping responses.

Similar to the fMRI analytic model, our VEP model is based on assembling a design matrix that is populated based on the exact onset times of the different multi-focal stimuli. We incorporate jitter to the interval between each stimulus to produce a semi-random onset sequence. The model also allows us to set a range of temporal frequencies to be used when the GLS is solved by incorporating a set of basis functions. Based on the spectral decomposition of the ISCEV VEP response templates, we have *a priori* knowledge to constrain the model to be only sensitive to frequencies in the 0-30Hz range and not to be confused by significant 60Hz line noise components or a substantial portion of EMG artifacts in the measured EEG. If a set of basis functions is not used, one could potentially obtain a similar effect by

applying a digital filter (band pass or low pass, etc.) to the raw EEG measurements for removing 60Hz line noise, etc. before solving the model. Furthermore, it is crucial to use exact onset times, which are calculated based on the timestamps of codes broadcasted via the parallel port of the stimulus presentation computer, as well as the measurement of the time offset between sending these codes and the analog output of a photodiode facing the TV or monitor being used to present the stimuli.

We have extensively validated the solution of the GLS model in Matlab through the use of synthetic data, and optimized the solution of the GLS model through the use of sparse matrix computations, as well as employing the graphics card (GPU) for analytical computations. In some cases, the speedup is almost 100x compared to solving the linear system of equations on the central processing unit (CPU) of the computer. This capability will enable us to continuously compute the VEP responses during data acquisition, which will make it possible to terminate a stimulus sequence early if the VEP responses are of sufficient quality. In future, we plan to use the gaze and eyelid opening measurements acquired simultaneously from the Smart Eye head and eye tracker to prune data points from the raw EEG in order to exclude time intervals during which the subject has not been looking at the fixation target (red circle) or blinked/closed his/her eyes.

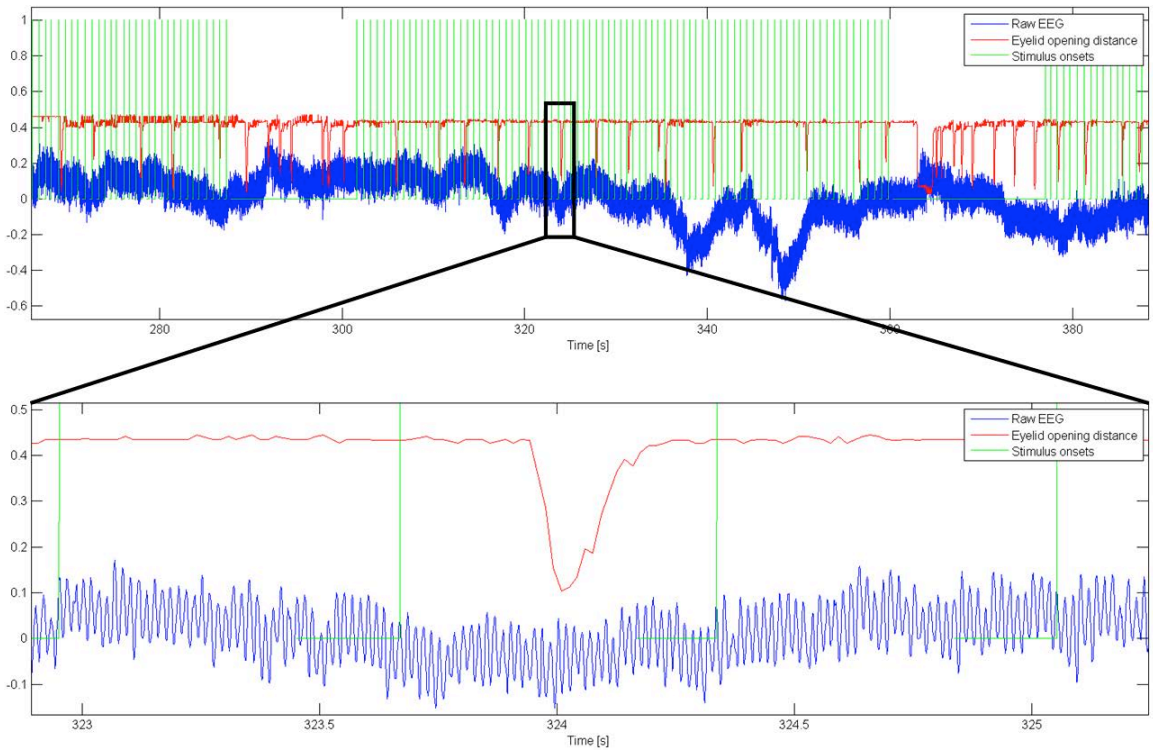


Figure 9. Example of a raw EEG signal from an occipital scalp location (blue time series) during a 60s pattern onset/offset stimulus sequence (from t=300s to t=360s in the top figure, and zoomed in at t~324s in the bottom figure), consisting of about 84 stimulus presentations. The red time series represents the size of the subject's left and right combined eyelid opening (i.e., maximum distance between the upper and lower eyelids), while each vertical portion of the green time series represents the exact time of each stimulus onset, based on the analog output from the photo diode facing the TV.

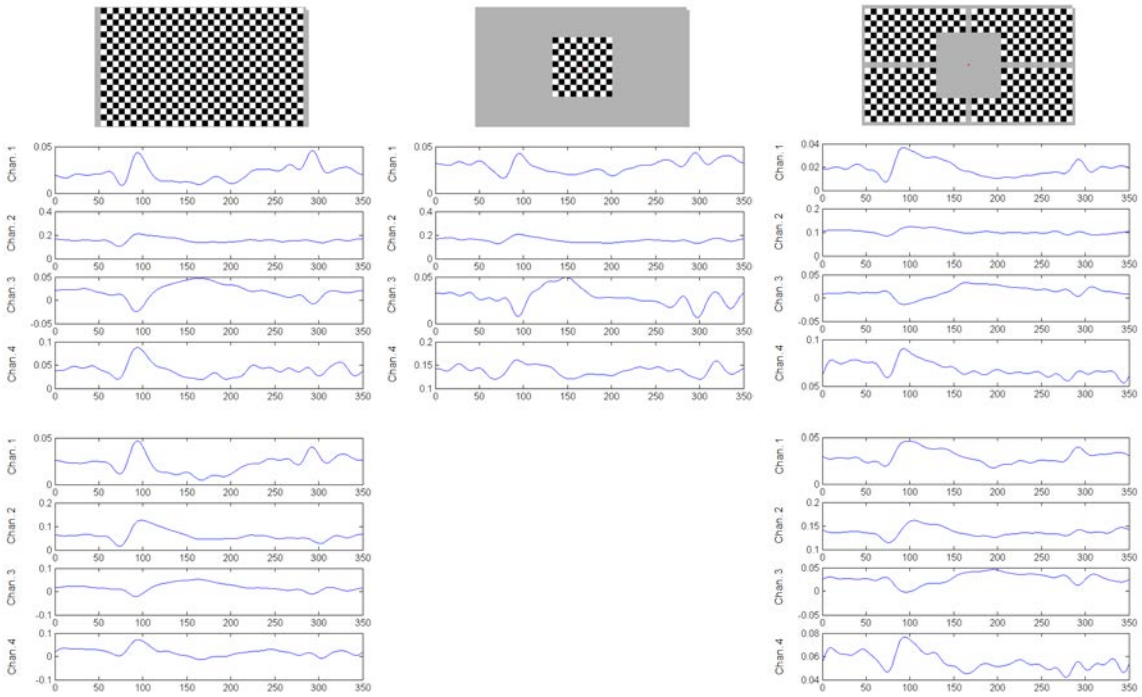


Figure 10. 350ms duration length VEP responses extracted for four (4) EEG channels for full-field (left column), center-only (middle column), and peripheral-only (right column) stimulus sequences consisting of ~84 stimulus presentations (over 60s) to test the reproducibility of the extracted VEP responses with our GLS-based analysis method. The full field and peripheral-only sequences were presented twice in two different stimulus runs (top vs. bottom half), and the wave forms are qualitatively highly correlated when comparing the two runs within each stimulus sequence type.

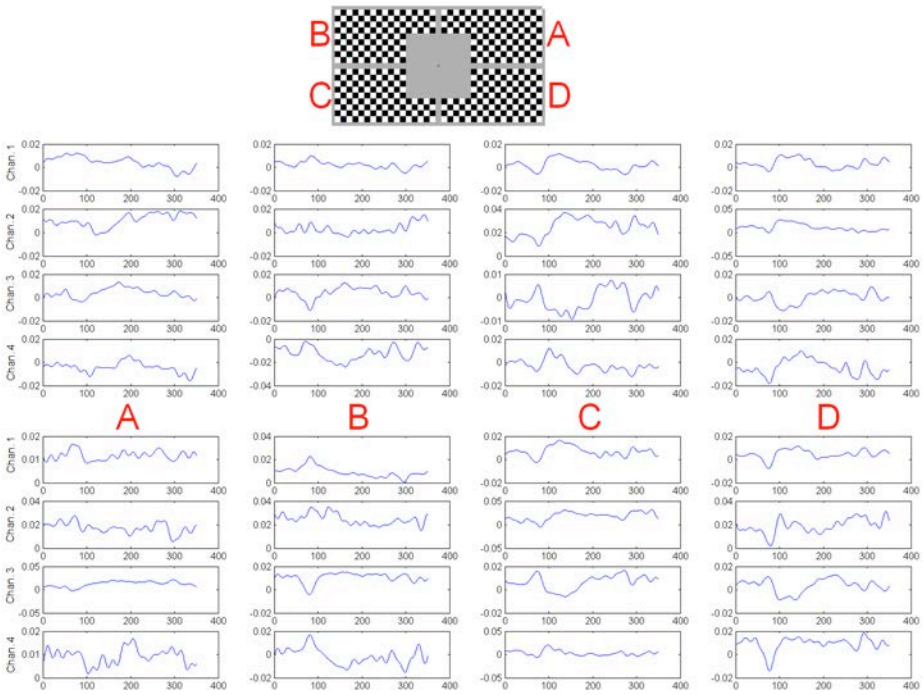


Figure 11. 350ms duration length VEP responses extracted for four (4) EEG channels for the peripheral-only stimulus sequence consisting of ~84 simultaneous and overlapping presentations at each of the four (4) peripheral locations/quadrants (over 60s) to test the reproducibility of the extracted VEP responses with our GLS-based analysis method. The sequence was presented twice on two separate test runs (top vs. bottom half), and the wave forms are qualitatively highly correlated when comparing the two runs within each stimulus location (i.e., column-wise).

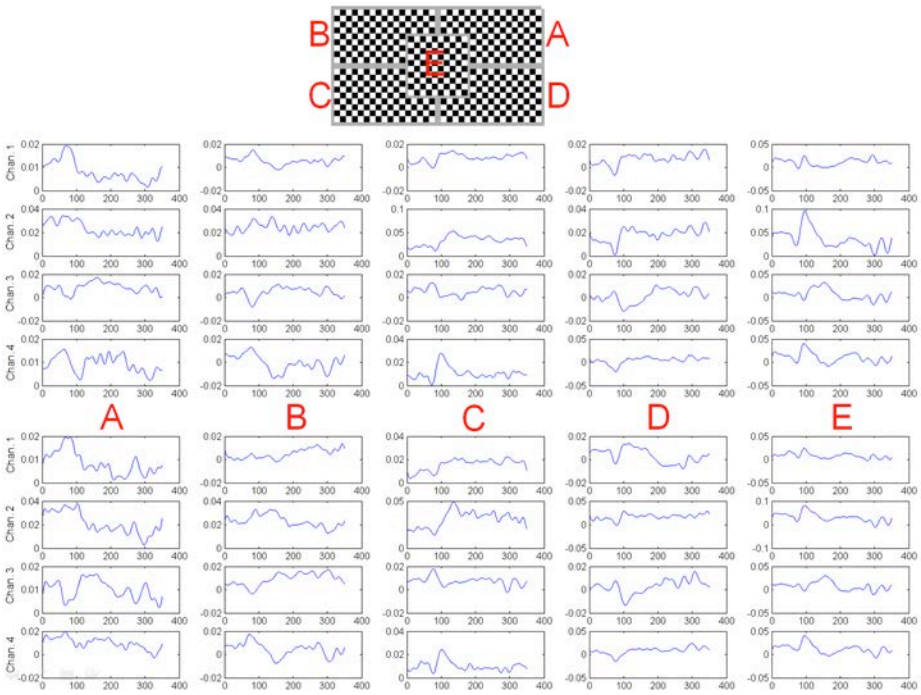
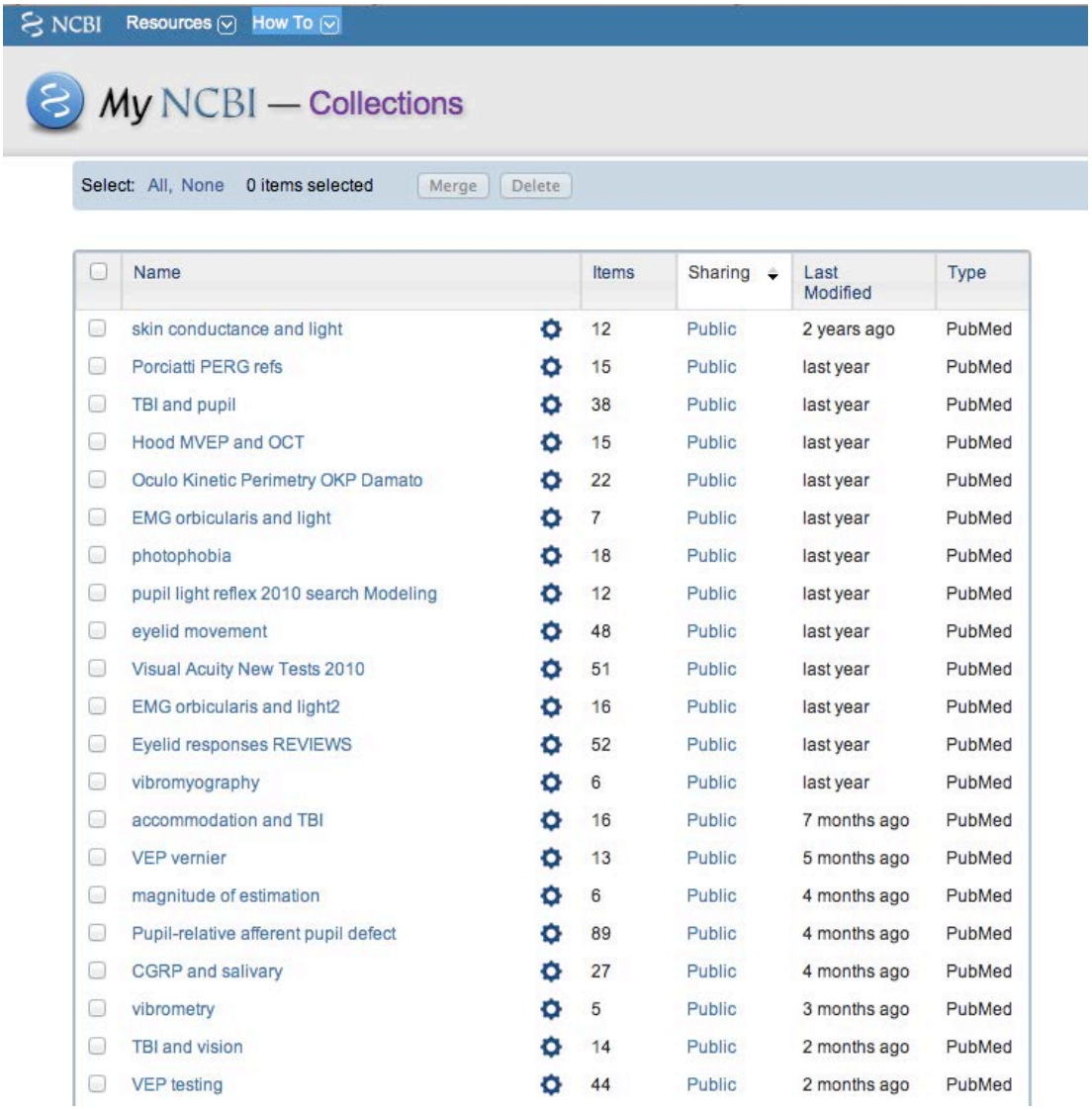


Figure 12. 350ms duration length VEP responses extracted for four (4) EEG channels for the central-peripheral stimulus sequence consisting of ~84 simultaneous and overlapping presentations at each of the five (5) stimulus locations (over 60s) to test the reproducibility of the extracted VEP responses with our GLS-based analysis method. The sequence was presented twice on two separate test runs (top vs. bottom half), and the wave forms are qualitatively highly correlated when comparing the two runs within each stimulus location (i.e., column-wise). The responses for the center stimulus location (column E) are qualitatively similar to the responses for the center-only stimulus sequence shown in an earlier figure.

1e. Literature study (months 1-12)

Completed in year 1 and reported in Year 1 annual report:



Name	Items	Sharing	Last Modified	Type
skin conductance and light	12	Public	2 years ago	PubMed
Porciatti PERG refs	15	Public	last year	PubMed
TBI and pupil	38	Public	last year	PubMed
Hood MVEP and OCT	15	Public	last year	PubMed
Oculo Kinetic Perimetry OKP Damato	22	Public	last year	PubMed
EMG orbicularis and light	7	Public	last year	PubMed
photophobia	18	Public	last year	PubMed
pupil light reflex 2010 search Modeling	12	Public	last year	PubMed
eyelid movement	48	Public	last year	PubMed
Visual Acuity New Tests 2010	51	Public	last year	PubMed
EMG orbicularis and light2	16	Public	last year	PubMed
Eyelid responses REVIEWS	52	Public	last year	PubMed
vibromyography	6	Public	last year	PubMed
accommodation and TBI	16	Public	7 months ago	PubMed
VEP vernier	13	Public	5 months ago	PubMed
magnitude of estimation	6	Public	4 months ago	PubMed
Pupil-relative afferent pupil defect	89	Public	4 months ago	PubMed
CGRP and salivary	27	Public	4 months ago	PubMed
vibrometry	5	Public	3 months ago	PubMed
TBI and vision	14	Public	2 months ago	PubMed
VEP testing	44	Public	2 months ago	PubMed

Figure 13. Example of literature search on topics in PubMed that was performed.

The literature search is an ongoing process, however, as we continually are updating our information with recently published articles that are relevant to our proposed research.

Task 2. In normal eyes, collect, correlate, and define normative range of values for both objective and standardized tests (months 13-18, now anticipated to occur in months 24-36):
2a. Pupil light reflexes (revised; months 24-36)
2b. Evoked potentials (revised; months 24-36)

2c. Eye movements to targets changing in resolution (revised; months 24-36)
2d. Standard light threshold perimetry (revised; months 24-36)

In year 2 we submitted the forms and protocol to our local IRB3 Human Use Committee and finally did receive the IRB-approval, and this was followed by final approval by Brigit Ciccarello after submission to ORP HRPO after their second-level review and approval was received. This occurred in the last quarter of year 2, which took longer than anticipated, putting us a year behind schedule in the planned human testing of normal subjects and patients with anterior pathway disorders (Task 3, below). During year 2, while awaiting human use approval, we took advantage of this time to further refine our software and hardware capabilities for testing the pupil light reflex, visual evoked potentials from the eye and visual cortex, and eye movement tracking to vanishing optotypes.

It is anticipated that in November 2012 all equipment will be set up in clinical testing suite in the Ophthalmology Department at the University of Iowa, where normal subjects and patients will be tested, as planned. Because it took longer for human use approval than anticipated and also because the software and hardware development took almost a full year longer, we are anticipating that we will need a one year, no cost extension of the grant starting in October 2013 in order to complete all of the planned testing (see SOW below).

Task 3. In eyes with damage to the retina or optic nerve, collect, correlate, and define normative range of values for both objective and standardized tests (revised; months 37-46):
3a. Pupil light reflexes (revised; months 37-46)
3b. Evoked potentials (revised; months 37-46)
3c. Eye movements to targets changing in resolution (revised; months 37-46)
3d. Standard light threshold perimetry (revised; months 37-46)

Task 4. In eyes with damage to primary visual cortex (V1), collect, correlate, and define normative range of values for both objective and standardized tests (revised; months 40-46):
4a. Pupil light reflexes (revised; months 40-46)
4b. Evoked potentials (revised; months 40-46)
4c. Eye movements to targets changing in resolution (revised; months 40-46)
4d. Standard light threshold perimetry (revised; months 40-46)

Task 5. Optimize hardware systems and vision testing protocols to reduce testing time, maximize the signal/noise, and minimize cognitive demands placed on the patient for proposed objective tests (revised; months 24-36):
5a. Develop robust discriminators of visual pathway dysfunction and location by testing normal participants and those with well-defined visual field defects from damage to specific sites in their visual pathway (e.g. retina, optic nerve, post-geniculate homonymous damage) (revised; months 40-46)

5b. Optimize signal to noise by informed selection of visual stimuli and innovative analysis approaches (revised; months 40-46)

KEY RESEARCH ACCOMPLISHMENTS (SUMMARY)

- Evaluation of and implementation of new desktop, binocular pupillometer with new chromatic pupil testing platform and anticipated delivery of fully portable binocular head worn unit by Neuroptics in Year 3
- Prototype dry electrode wireless system delivered in Year 2 and is currently being implemented with software interface
- Visual stimulus presentation hardware system and software platform developed for delivery of stimuli and on-line analysis of visual evoked responses from visual cortex (regional visual field stimulation and analysis), eye movement following of vanishing optotypes, and simultaneous pupil responses.

REPORTABLE OUTCOMES

Since the first two years of this research was restricted to implementation of a hardware and software testing and analysis platform, we have not yet tested human subjects (years 3 and 4). Human approval was granted in the last quarter of year 2. Therefore, we do not yet have results of testing to report in the literature. However, the following two manuscripts were published on relevant work to this project for using the pupil light reflex to chromatic stimuli to diagnose and characterize photoreceptor disease of the retina:

1: Kawasaki A, Crippa SV, **Kardon R**, Leon L, Hamel C. Characterization of Pupil Responses to Blue and Red Light Stimuli in Autosomal Dominant Retinitis Pigmentosa due to NR2E3 Mutation. Invest Ophthalmol Vis Sci. 2012 Aug 15;53(9):5562-9. Print 2012 Sep. PubMed PMID: 22807301.

2: Kawasaki A, Munier FL, Leon L, **Kardon RH**. Pupillometric quantification of residual rod and cone activity in leber congenital amaurosis. Arch Ophthalmol. 2012 Jun;130(6):798-800. PubMed PMID: 22801849.

CONCLUSIONS

The research work that we are carrying out has important implications for the greater public good, in addition to its military relevance. Visual impairment from traumatic brain injury can occur in military personnel exposed to direct trauma to the brain or indirectly from blast injury. Similar damage to the visual system can also occur in the civilian population from TBI resulting from motor vehicle accidents and also from head injury due to contact sports at both the school and professional level. Traumatic causes of visual damage can also be additive after repeated episodes of head injury. Patients with visual pathway damage are often unaware of

the problem and their associated cognitive impairment may mask the underlying vision impairment and also prevent detection with standard tests of visual function, which require good cognitive performance and focused attention during the test. In addition, other forms of cognitive impairment in the general population such as attention deficit disorder, depression, and dementia prevent the accurate assessment of visual function. Patients with undiagnosed visual dysfunction and superimposed cognitive impairment may pose a danger to themselves and to others when tasks such as driving and other tasks, which demand good visual performance, cannot be safely carried out.

For this research, our main goal is to use objective reflexes of the visual system to diagnose vision deficits and ensure effective monitoring of their treatment, when indicated. Such tests will allow accurate testing of the visual system with almost no demands on cognitive function during testing. This will be possible because the constriction of the pupils in response to light, the electrical recording of light evoked potentials (voltage) from the skin overlying the vision centers of the brain and the monitoring of purposeful eye movements to track moving targets are all objective, natural reflexes of the visual system. We are taking advantage of these reflexes by implementing an integrated system to quantify them using a specially designed suite of rapidly performed tests requiring little patient cooperation. Once validated in our proposed study, these tests can be used in cognitively intact or cognitively impaired individuals to assess visual function, leading to rehabilitation and treatment when appropriate.

The availability of the objective tests of vision being developed and implemented will greatly improve eye care by providing faster, lower cost testing that can be performed in remote settings. This will provide easier access of the public to accurate assessment of their visual function and will also reduce the cost associated with current testing and transportation to sites of testing. Such tests will also provide a new tool for assessing innovative treatments being developed to save or restore vision.

REFERENCES - none

APPENDICES – none

SUPPORTING DATA – all figures including in body of report